Leptomeningeal dissemination in children with progressive low-grade neuroepithelial tumors

Juliette Hukin,¹ Joao Siffert, Linda Velasquez, David Zagzag, and Jeffrey Allen

Division of Neurology, Department of Pediatrics, Children's and Women's Hospital, Vancouver, British Columbia, Canada V6H3V4 (J.H.); Institute of Neurology and Neurosurgery, Beth Israel Medical Center, New York, NY 10128 (J.S., L.V., J.A.); and New York University Hospital, New York, NY 10016 (D.Z.)

Our purpose is to describe the incidence and clinical features of leptomeningeal dissemination (LM) in children with progressive low-grade neuroepithelial tumor (LGN). We have continuously tracked all patients with primary CNS tumors since 1986. Satisfactorily followed data were obtained on 427 of the 588 patients with localized LGN at diagnosis between 1986 and 1998, 177 (42%) of whom developed progressive or recurrent disease. LM was identified in 13/177 (7%). The median age at initial diagnosis was 5 years and at LM diagnosis was 8.5 years. The primary tumor sites were diencephalon (6), brainstem (3), cerebellum (2), cerebrum (1), and spinal cord (1). The histologies were pilocytic astrocytoma (4), ganglioglioma (4), fibrillary astrocytoma (3), mixed glioma (1), and glioneurofibroma (1). Management included chemotherapy (2) or radiotherapy (3) or both (7); 1 patient received only radical resections of symptomatic lesions. The 5-year progression-free survival rates for patients with localized versus LM disease at recurrence were 22% (95% confidence interval [CI], 13%-25%) versus 15% (95% CI, 0.1%-36%), respectively ($P = 0.28$). The 5- and 10-year overall survival rates for patients with localized disease versus LM were 87% (95% CI, 82%-92%) and 83% (95% CI, 77%-89%) versus 68% (95% CI, 39%-91%) and 68% (95% CI, 39%-91%), respectively ($P = 0.05$). The 7% incidence of LM is a low estimate because patients were not routinely staged at recurrence. Tumors arising from the diencephalon appeared to predispose to LM; no other predisposing features were identified. We strongly urge that for optimum treatment planning all

patients with recurrent LGN be staged with an enhanced spine and brain MRI before adjuvant therapy is initiated. The good survival of patients with LGN and LM reflects a more indolent disease than malignant CNS tumors with LM. *Neuro-Oncology* 4, 253-260, 2002 (Posted to *Neuro-Oncology* [serial online], Doc. 01-068, June 27, 2002. URL <neuro-oncology.mc.duke.edu>)

LGNs² are the most common primary CNS tumor in children, representing 50% to 60% of cases. They typically arise from the cerebellum, temporal lobe, chiasm/hypothalamus, and less frequently, the brainstem and spinal cord. LGNs typically manifest a low proliferative rate (mitotic index of less than 1.5%) and exhibit a favorable prognosis. In those with tumors amenable to a gross total surgical resection, the 10-year survival exceeds 90% (Campbell and Pollack, 1996; Pollack et al., 1995). A lower 10-year survival (50% to 86%) prevails in those patients for whom an incomplete resection is achieved (Campbell and Pollack, 1996; Scott and Mickle, 1987; Woo et al., 1988). Recurrence patterns include the primary site, metastases, or both. The reported incidence of LM at recurrence varies from 3% to 10% (Civitello et al., 1988; Mamelak et al., 1994; Pollack et al., 1994). The true incidence of LM is unknown owing to the absence of routine staging. Metastatic spread of a primary malignant CNS tumor implies more aggressive behavior and a worse prognosis; however, the significance in the setting of LGN is not well established.

The aims of this study are to describe the frequency of dissemination in LGN at recurrence in our large institutional pediatric neuro-oncology database; to identify whether patients with LM at recurrence have unique clinical or histologic features; and to discern the impact of LM on therapy and survival.

Methods

A total of 601 patients with LGN were identified in our database of 1767 pediatric primary CNS tumor patients

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¹Address correspondence and reprint requests to Juliette Hukin, K3, Division of Neurology, Children's and Women's Hospital, 4480 Oak St., Vancouver, BC, Canada V6H3V4.

²Abbreviations used are as follows: CI, confidence interval; LGN, low-grade neuroepithelial tumor; LM, leptomeningeal metastasis; PFS, progression-free survival.

cared for by our service from 1986 to 1998. The database was started at New York University Medical Center and continued after the authors moved to Beth Israel Medical Center in 1996. Both institutions are tertiary care facilities. Inclusion criteria were as follows: age less than 21 years; tissue confirmation of LGN, including astrocytoma and mixed glial and neuronal neoplasms. Ependymomas and diffuse pontine gliomas were excluded. The term hypothalamus was allocated to all tumors arising from the hypothalamus/optic chiasm region because it is sometimes difficult to delineate the precise location of the chiasm. LM was defined by several criteria: neuroimaging, clinical neurologic signs, cerebrospinal fluid cytology, or biopsy confirmation. The use of MRI alone to establish the diagnosis of LM was used only if nodular enhancing abnormalities were noted separate from the primary tumor on MRI performed either before or more than 2 weeks after a neurosurgical procedure. Charts were reviewed regarding demographics, tumor location, histology, treatment, and survival. Follow-up was obtained in the clinic or by phone survey. Statistical analysis of PFS and overall survival was performed using the Kaplan-Meier procedure and log-rank tests to test the hypothesis that patients with LM did not differ from those with localized LGN at recurrence. Patients who had had no follow-up in the previous 3 years were excluded from the analysis of survival to avoid bias from inadequate recent follow-up.

Results

Of the 601 LGNs identified, 588 had localized disease at diagnosis, and 13 (2%) had LM at the time of diagnosis. Satisfactory follow-up was obtained in 427 of 588 patients with localized disease. Of the 427, 177 (73%) patients progressed; LM was apparent in 13 (7%) at progression. Evidence of LM was noted on MRI in all 13 cases. Eight children had signs and/or symptoms suggestive of LM, such as paraparesis, sphincter dysfunction, hydrocephalus, ataxia, seizures, and cognitive dysfunction.

In 4, the primary tumor was symptomatic at the time of progression and the LM was an incidental finding. Only 1 patient had LM at progression, identified as an incidental finding on surveillance imaging. Tissue confirmation of LM was made in 7 patients (3 at autopsy only). Cerebrospinal fluid cytology was confirmatory in only 1 of the 6 patients in whom the cerebrospinal fluid was examined. The male-to-female ratio was equal in both those with localized disease and those with LM. The median age at initial diagnosis was 7.1 years (range, 0.1-20.9 years) in those without recurrence, 6.2 years (range, 0.1-20.9 years) in those with localized recurrence, and 5 years (range, 0.3-20.4 years) in those with LM at recurrence. The Kuskal-Wallis analysis for the median age showed no significant difference between the 3 groups ($P = 0.16$). The median age at the time of diagnosis of LM was 8.5 years (range, 2.7-22.8 years). Primary tumor site, histology, metastatic site, and age at diagnosis in 13 patients with LM at progression are outlined in Table 1.

Histology

The distribution of histologic subsets of 427 LGNs with adequate follow-up are outlined below. Of these, 164 recurred locally and 13 were LMs. There was an expected distribution of various LGNs, with pilocytic astrocytomas at 28% (120/427), low-grade fibrillary astrocytomas at 36% (152/427), gangliogliomas at 23% (96/427), and mixed gliomas at 5% (19/427), these being the more commonly represented subsets. The recurrence rates of the most common histologic types were similar, varying between 40% and 47%. Of 30 dysembryoplastic neuroepithelial tumors, 6 oligodendrogliomas, and 3 others including ganglioneurocytoma and glioneurocytoma, there were 16 localized recurrences and no LM recurrences. The frequency of LM in the various histologic criteria are as follows: pilocytic astrocytoma 3% (4/120),

Table 1. Primary tumor site, histology, metastatic site, and age at diagnosis in 13 patients with LM at progression of LGN

Patient no.	Age at diagnosis (yrs.)	Age at LM diagnosis (yrs.)	Histology	Primary tumor location	Location of metastasis		Extent of metastasis	
					Brain	Spine	Single	Multiple
1	0.3	8.1	Mixed glioma	Diencephalon	+	+		+
2	0.6	4.1	Ganglioglioma	Diencephalon	+	+		+
3	1.3	2.7	JPA	Diencephalon	+	+		+
4	2.1	2.9	Fibrillary astrocytoma	Diencephalon		+	+	
5	3	6.4	Ganglioglioma	Brainstem	+			+
6	3.7	8.5	JPA	Cerebellum		+	+	
7	5	6.8	JPA	Diencephalon		+	+	
8	8.2	9	Ganglioglioma	Cerebral	+			+
9	8.2	9.3	Glioneurofibroma	Spinal cord	+			+
10	9.3	14.9	JPA	Left cerebellar hemisphere	+			+
11	11.7	13	Ganglioglioma	Medulla	+	+		+
12	14.7	15.8	Fibrillary astrocytoma	Diencephalon	+	+		+
13	20.4	22.8	Fibrillary astrocytoma	Brainstem (unilateral pontine exophytic lesion)	+	+		+

Abbreviation: JPA, juvenile pilocytic astrocytoma.

low-grade fibrillary astrocytoma 2% (3/152), ganglioglioma 4% (4/96), mixed glioma 5% (1/19), and 1/1 glioneurofibroma. Of the 177 patients with recurrences, mixed gliomas, gangliogliomas, and pilocytic astrocytomas were the most frequent to disseminate, at 11% (1/9), 10% (4/39), and 8% (4/48), respectively. Low-grade fibrillary astrocytoma disseminated the least frequently at 5% (3/64).

Tumor Location

Among the 427 patients with LGN, the most common primary tumor location was as expected in the posterior fossa (38%, 163/427 patients). Other common sites included cerebral cortex (20%, 84/427), hypothalamus (17%, 74/427), spinal cord (19%, 82/427), and thalamus (3%, 14/427). The 10 remaining tumors arose from the pineal region ($n = 3$) and the lateral ($n = 2$) or third ($n = 5$) ventricle; 2 had a localized recurrence. The relatively high number of spinal cord tumors as the primary site in this series likely relates to the referral pattern to our institution. Nine patients with diencephalic tumors had neurofibromatosis type 1, and none of these patients had LM. The recurrence rates by primary tumor location varied between 32% and 50% in this cohort. The frequency of LM when categorized by primary tumor site was as follows: posterior fossa 3% (5/163), cerebral cortex 1% (1/84), diencephalic region 7% (6/88), and spinal cord 1% (1/82). Of patients who progressed, those with a diencephalic tumor were at greatest risk of disseminating, at 14% (6/43). The risk of LM at recurrence in the other affected groups was as follows: posterior fossa 7% (5/68); cerebral cortex 4% (1/26); and spinal cord 3% (1/38).

Sites of Leptomeningeal Metastases

All LM lesions were enhanced by gadolinium on MRI. Six patients had both brain and spinal metastases. Four

had only distant metastases within the CNS, for example, a primary diencephalic tumor with only spinal metastases. Of these, 3 of the patients' metastases were symptomatic. Fig. 1 shows a typical case of a primary brain tumor with only brain metastases.

Treatment

The group of patients reviewed were diagnosed over a 12-year span, and management has evolved over this period of time. Table 2 shows the details of management of each of the disseminated patients. Carboplatin-based chemotherapy was the first line of chemotherapy. Second-line chemotherapy was nitrosourea based in 3 and temozolomide in 1 patient. Table 3 outlines a comparison of therapies of those without recurrence and those with and without LM at progression. Initial radical surgery was far more common in patients who did not have a recurrence; 50% (126/250) had a gross total resection (95% CI, 44%-57%). When comparing patients who had a local recurrence or dissemination at recurrence, the rate of gross total resection was 19% (31/164) (95% CI, 13%-25%) and 8% (1/13) (95% CI, 0.1%-36%), respectively, confirming previous reports that if a gross total resection is achieved at diagnosis of LGN, the risk of recurrence is reduced. Ninety-two percent (12/13) of the LM group received adjunctive therapy; the 1 remaining had radical resections of symptomatic lesions only. Adjuvant therapy was not commonly used in the absence of recurrence.

Morbidity

Table 4 demonstrates the status of patients with LM at the time of last follow-up. Of the 9 patients who were alive, 3 had significant endocrine dysfunction, 2 had mild-to-moderate cognitive dysfunction, 4 had severe physical disabilities, and only 1 was asymptomatic. Of those who

Fig. 1. Axial (A) and sagittal (B) views of T1-weighted MRIs of gadolinium-enhanced occipital lobe pilocytic astrocytoma with LM at progression.

Table 2. Treatment and survival of patients with LM

Patient no.	Surgery	Radiotherapy	Chemotherapy (response)	Symptoms of LM	PFS (mos.)	Overall survival (mos.)
1	PR	IF	CDBP, VCR ^a (stable 41 mos.); TPCV ^c		93	144+
2	STR × 4, GTR, Bx	IF	CDBP, VCR ^a (stable 13 mos.)		42	56
3	PR	IF	CDBP, VCR (partial 25 mos.); temozolomide ^a (partial 5+ mos.)	+	39	58+
4	Bx	—	CDBP, VCR ^a (partial 21 mos.), TPCV ^c (stable 8+ mos.)		21	50+
5	GTR, STR	IF	CDBP, VCR ^a (partial 15+ mos.)	+	41	88+
6	GTR × 2, shunt	—	—	+	57	72+
7	STR × 3, shunt	IF	—	+	78	93+
8	STR, Bx, shunt, PR	—	CDBP, VCR ^a (partial 24 mos.); 6MP, CCNU, procarbazine ^c (stable 20 mos.); VP16 ^d (stable 21 mos.); taxatere ^e		10	74+
9	STR × 2, shunt	IF	—		23	29
10	STR × 5, shunt	IF	CDBP ^a (complete response 28+ mos.)	+	4	120 ^e
11	PR, shunt	IF + CS ^a	CDBP, VCR ^a (progression 12 mos.)	+	12	40
12	STR, Bx	IF + CS ^a	—	+	24	120+
13	STR × 2, shunt	IF	VP16, CDBP, BCNU, thioguanine ^a (progression 10 mos.)	+	31	53

Abbreviations: Bx, biopsy; CCNU, lomustine; CDBP, carboplatin; CS, craniospinal; GTR, gross total resection; IF, involved field; 6MP, 6-mercaptopurine; PR, partial resection; STR, subtotal resection; TPCV, thioguanine, procarbazine, lomustine, vincristine; VCR, vincristine; VP16, etoposide.

^aAt time of 1st relapse with dissemination.

^bAt time of 2nd relapse.

^cAt time of 3rd relapse.

^dAt time of 4th relapse.

^eCause of death, bacterial endocarditis.

Table 3. Initial surgery of localized LGN at diagnosis

Therapy	No progression	Localized disease at progression	LM
Initial therapy			
Biopsy	6% (15/250)	28% (46/164)	31% (4/13)
Partial resection	44% (109/250)	53% (87/164)	62% (8/13)
Gross total resection	50% (126/250)	19% (31/164)	8% (1/13)
Shunt insertion	14% (35/250)	32% (53/164)	54% (7/13)
Progressive disease therapy			
Partial resection		58% (95/164)	31% (4/13)
Gross total resection		30% (50/164)	15% (2/13)
Adjuvant therapy			
Chemotherapy	12% (29/250)	17% (27/164)	69% (9/13)
Radiotherapy	7% (18/250)	23% (38/164)	77% (10/13)

died, 1 died of disease unrelated to the tumor. The 3 patients who died of progressive tumor or surgical intervention for progression included those who had an exophytic unilateral pontine tumor, a hypothalamic tumor diagnosed at less than 1 year of age, and a cervical tumor.

Survival

We compared the survival of those who had a localized progression to those who had dissemination at the time of progression. The median follow-up was 6 years (range, 0.5-30 years). The 5-year PFS in the LM group was 15% (95% CI, 0.1%-36%) versus 22% (95% CI, 13%-25%) in those who progressed only at the primary site (see Fig. 2). There was no statistically significant difference in

PFS between the 2 groups. The 5- and 10-year overall survival rates in the LM group were 68% (95% CI, 39%-91%) and 68% (95% CI, 39%-91%) versus 87% (95% CI, 82%-92%) and 83% (95% CI, 77%-89%), respectively, in those who progressed only at the primary site (see Fig. 3). By log rank, there was a statistical difference in overall survival ($P = 0.05$); however, because of the small size of the LM group, we must be cautious in this interpretation.

Discussion

LM in children with LGN is rare, but probably under diagnosed. In our series, we documented LM in only 7%

Table 4. Morbidity of survivors of LGN with LM

Patient no.	Neurologic status at follow-up	Endocrine dysfunction	Cognition	Disability status	Disease status	Radiology status
1	Blindness, optic neuropathy	Hypothal dys	Normal	Independent	Progressing	LM
2	Normal	GH, DI	Normal	—	Died of postoperative hemorrhage; autopsy: LM	—
3	Normal	Panhyp	Normal	Independent	Stable	LM
4	Normal	Normal	Normal	Independent	Stable	Stable hypothalamic lesion
5	Mental retardation	Normal	Moderate mental retardation	Dependent, chronic pain	Stable	LM
6	Paraparesis, right facial paresis	Normal	Normal	Bed bound	No tumor	No tumor
7	Paraparesis, dysphasia	Panhyp	Learning disability	Independent, walking	Stable	Small residual nodule
8	Parinaud's syndrome	Normal	Normal	Independent	Progressing	LM
9	Quadriparesis dysphagia, respiratory failure	Normal	Normal	—	Died of tumor; autopsy: LM	—
10	Severe behavioral dysfunction	Normal	Normal IQ, social immaturity	—	Died of bacterial endocarditis; autopsy: no tumor	—
11	Quadriparesis	Normal	Normal	—	Died	LM, progressive disease
12	Expressive aphasia	Hypothyroidism	Poor short-term memory	Independent, less stamina, graduating from college	Stable	LM
13	Paraparesis	Normal	Mild impairment	—	Died of sepsis; autopsy: LM	—

Abbreviations: DI, diabetes insipidus; GH, growth hormone deficiency; Hypothal dys, hypothalamic dysfunction; Panhyp, panhypopituitarism.

Fig. 2. Kaplan-Meier progression-free survival curves of those patients who progressed locally versus those who progressed with dissemination.

(13/177) at the time of progression. MRI confirmation was used in 13 cases and histologic documentation of LM in 8. Only 8 were symptomatic from the leptomeningeal disease. The true incidence will remain unknown until routine staging is performed on all LGNs

at recurrence and at initial diagnosis. LM at progression of LGN is associated with a worse overall survival than it is in those with a localized recurrence. However, the prognosis remains favorable in disseminated LGN when compared with malignant CNS tumors with LM.

Fig. 3. Kaplan-Meier overall survival curves of those patients who progressed locally versus those who progressed with dissemination.

There are 22 clear pediatric cases of LM at progression in the published literature (Civitello et al., 1988; Doireau et al., 1999; Mamelak et al., 1994; McCowage et al., 1996; Mishima et al., 1992; Patt et al., 1999; Tamura et al., 1998). Our experience not only substantially increases the experience reported to date, but also provides a crude estimate of the incidence. The high incidence in our population (7%) in this contemporary series may reflect the recent availability and the sensitivity of enhanced MRI. The median age at diagnosis among the previously published cases was 5 years (range, 0.5-19 years), as it was in our study (range, 0.3-20.4 years). The median interval to detection of dissemination was 1.75 years (range, 0.5-8.5 years), similar to our series in which the median time to progression was 2 years (range, 0.3-8 years). Of the 22 published cases, 68% were pilocytic astrocytomas, and 43% arose primarily from the hypothalamus. Among our group, 54% were low-grade gliomas of either the fibrillary or pilocytic type, and 46% arose primarily from the diencephalon. The published 22 cases were treated with radiotherapy (9), chemotherapy (17), surgery to symptomatic lesions alone (1), and one patient preferred no treatment. The median follow-up of the 22 cases from the time of documented dissemination was 27 months (range, 7-72 months). Five patients died of progressive disease, and 1 died from a long-term complication of chemotherapy. Our median follow-up was 41 months (range, 6-116 months). Four patients died of tumor, and 1 died because of infection unrelated to therapy.

It is not clear that any specific form of therapy extends life for LGN patients with LM, but some measures may decrease morbidity or relieve suffering. Surgical treatment of selective symptomatic lesions may provide prolonged palliation. Eight of our 13 patients were ineligible for craniospinal radiation because they were noted to have dissemination after involved-field radiation. This underscores the importance of staging LGNs at least before undertaking radiotherapy because the evidence of LM may alter treatment planning. Craniospinal radiation can be effective in stabiliz-

ing disseminated LGN for more than 8 years. Chemotherapy was effective in our series to varying degrees. Responses varied from stabilization to a complete response in 9 of 12 courses completed. Response to carboplatin-based therapy in 9 patients was as follows: complete response, 1; partial response, 4; and stable disease, 2; with a median PFS of 25 months (range, 10-41+ months). This is a similar response rate to previous reports for localized low-grade gliomas (Packer et al., 1997; Prados et al., 1997), where response rates of 56% and 36%, respectively, were described. Packer reported that 4% of his series of 78 patients had disseminated disease and Prados et al. did not report any in their series of 42 patients. This suggests that chemotherapy is a reasonable initial approach in an attempt to at least delay radiotherapy and its adverse effects. LM of LGNs tends to grow more slowly than do malignant primary CNS tumors with LM, such as primitive neuroectodermal tumors.

Of our patients with LM, 46% (6) had severe morbidity in terms of having cognitive dysfunction and/or being wheelchair bound due to extensive tumor (4), radiotherapy (2), or both. Dirven et al. (1997) described 11% of a series of 72 patients with cerebellar astrocytomas as having severe long-term neurologic deficits, and Scott and Mickle (1987) described 36% of 14 survivors with diencephalic tumors as having severe morbidity. Although patients with LM have a relatively good prognosis in terms of survival, there is a suggestion that the morbidity is greater than in those with only localized recurrences. This is likely a consequence of the greater extent of disease and more aggressive radiotherapy. Patients with a localized or disseminated recurrence have a similar PFS, although there is a suggestion of improved survival in those with localized disease by log-rank test.

This retrospective study has several limitations, which we will attempt to address below. Because patients with LGN were not routinely staged at our institution either at diagnosis or recurrence, our data may underestimate disseminated cases; in addition, some cases may have even had dissemination at diagnosis that was asymptomatic

and unrecognized. The advent of MRI technology has increased the recognition of dissemination in the past 10 years. The observation of enhancing nodules before surgery is a reliable indication of LM. Occasionally, a uniform pachymeningitis can be seen. It would have been preferable to confirm MRI evidence of dissemination by cytology or biopsy in all cases; however, in the presence of bulky metastatic disease, the morbidity associated with additional biopsy may not be warranted. It would have been preferable to obtain more recent follow-up in all our patients with primary localized LGN; however, these patients were often living in distant communities, so close follow-up at our institution was difficult. In addition, patients with uncomplicated LGNs who had an aggressive surgical resection were often not followed so closely, particularly in asymptomatic patients. The treatment of this small series of LM patients was heterogeneous, thus limiting our interpretation of the efficacy of the various treatment modalities used. The follow-up in our small series of LM patients was relatively short, thus the survival curves should be interpreted with caution. We would need larger numbers to be more definitive in our conclusions.

The underlying pathogenesis of LM is unclear. There is no histologic evidence to suggest that these tumors should behave any differently than those with localized disease. This unusual behavior may be related to differences in molecular genetic factors or to effects of certain growth factors or adhesion molecules (Brooks et al., 1994; Brown et al., 1997; Figarella-Branger et al., 1996; Jaworski et al., 1996). We are in the process of evaluating molecular factors that may play a role in cellular migration, proliferation, and adhesion of LGNs with leptomeningeal dissemination.

We suggest that caregivers of pediatric patients with LGN consider the remote possibility of LM when evaluating these patients at the time of diagnosis and at the time of progression. Although the low frequency in this series does not necessarily imply that all patients with LGN should have routine staging by MRI and

cerebrospinal fluid examination, this should be considered in selected patients. Patients who should definitely be staged with MRI include those with evidence of regional metastases or otherwise unexplained hydrocephalus, those with clinical evidence of remote metastases, and those in whom local disease control is being considered at the time of recurrence, particularly in terms of radiotherapy. One should also consider staging in those with primary diencephalic disease, as there appears to be a greater preponderance of dissemination in these patients (Civitello et al., 1988; Doireau et al., 1999; Mamelak et al., 1994; Mishima et al., 1992; Patt et al., 1999; Tamura et al., 1998). It would appear that LM may behave in an indolent fashion, so delay of diagnosis and therapy may not be a major disadvantage to the patient in terms of overall survival; however, it may be important in terms of reducing disease-related morbidity.

Conclusion

The 7% incidence of LM is likely a low estimate because patients were not routinely staged at our institution at recurrence. We have not identified any histologic or demographic features that are associated with the predisposition to develop LM at recurrence other than tumor site of origin (diencephalon). We strongly urge that all patients with recurrent LGN be staged with an enhanced spine and brain MRI before initiating adjuvant therapy for optimum treatment planning. The overall prognosis for patients with disseminated LGN at recurrence appears to be worse than the prognosis for patients with a localized recurrence, but far better than for patients with a malignant brain tumor with dissemination. Medical intervention in LGN with LM may improve quality of life by potentially delaying or reversing associated neurologic deficits. Future prospective studies are required to evaluate whether or not this is true.

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